



Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Panel's Recommendations

- The approach to evaluation and treatment of HIV-infected children on stable combination antiretroviral therapy with suspected or confirmed influenza should be similar to that of HIV-uninfected children **(AIII)**. HIV-infected children with evidence of moderate-to-severe immunosuppression by CD4-defined or clinical disease-defined categories may be at increased risk of influenza-related complications and should be monitored closely until illness resolution **(BII)**.
- Prevention of influenza in HIV-infected children aged 6 months and older should include annual administration of trivalent inactivated influenza vaccine, according to Advisory Committee on Immunization Practices recommendations (see annual updated recommendations at <http://www.cdc.gov/vaccines/pubs/acip-list.htm>) **(AII)**.
- Influenza-specific antiviral chemoprophylaxis should be considered for HIV-infected children based on level of immunosuppression and other preexisting co-morbidities, influenza vaccination status, and degree of exposure to suspected or confirmed influenza, according to CDC guidelines (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>) **(BII)**.
- HIV-infected children with confirmed influenza should be considered for prompt antiviral therapy, according to CDC guidelines (see <http://www.cdc.gov/flu/antivirals/> and <http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf>) **(AII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials *in children*[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Influenza viruses are spread directly from person to person across distances less than 6 feet via large or small droplets generated by coughing or sneezing or indirectly from contaminated surfaces to hands to mucosal membranes.¹ Influenza has an incubation period of 1 to 4 days (mean: 2 days),² and can be shed by adults from 1 day before to 5 to 10 days after onset of symptoms and by children from several days before to ≥10 days after illness onset.³ Viral shedding can occur over longer periods of time in those with chronic diseases, including patients with immunologic suppression or those receiving systemic corticosteroid therapy.⁴⁻⁷

Seasonal influenza viruses can be divided into three types: A, B, and C. Influenza A viruses are further subdivided based on surface glycoproteins: hemagglutinin (H) and neuraminidase (N). Influenza A viruses circulate primarily among aquatic birds, but also among humans and other animals, including pigs, horses, and seals. Influenza A subtypes H1N1 and H3N2 currently circulate among humans. Influenza B circulates primarily among humans.⁸ Influenza C circulates primarily among animals such as swine and dogs and rarely in humans.^{9,10} Influenza A and B cause seasonal outbreaks and impose a higher disease burden than influenza C, which is associated with milder illness, sporadic cases, and rarely, localized outbreaks. Two influenza A subtypes and one influenza B strain are included in current seasonal influenza vaccines. Influenza viruses cause annual outbreaks in the United States lasting from winter through early spring.

Certain groups have been identified by the Centers for Disease Control and Prevention (CDC) to be at risk of complications from influenza, including individuals with immunosuppression caused by HIV infection.¹¹ The burden of influenza virus in HIV-infected children has been characterized in limited case reports and case series, but assessment of its impact has been confounded by the stage of HIV infection, type of antiretroviral therapy (ART), and other comorbidities.¹² In the era before combination antiretroviral therapy (cART), multiple large epidemiological studies suggested high hospitalization and mortality rates with influenza in HIV-infected

individuals.^{13,14} However, observations reported during the cART era suggest that better control of HIV infection is associated with a milder course of influenza. In an outbreak of 2009 H1N1 influenza virus infection in Germany involving 15 HIV-infected schoolchildren receiving cART, the clinical course in HIV-infected children was similar to that in HIV-uninfected children.¹⁵ A case series of 13 HIV-infected children with 2009 H1N1 in Barcelona also reported outcomes similar to those in HIV-uninfected groups.¹⁶ In both reports, half of the children were aged <13 years, had CD4 counts >500 cells/mm³, and very low or undetectable HIV viral loads. Existing data suggest that HIV-infected children receiving cART who have natural influenza infection develop influenza-specific antibody levels similar to those seen in HIV-uninfected children.¹⁵ Larger observational studies of HIV-infected children are needed to further substantiate these findings.

Clinical Manifestations

Signs and symptoms related to influenza are similar between HIV-infected and HIV-uninfected children and include fever, cough, and rhinorrhea in the majority of patients.¹⁵⁻¹⁷ Loss of appetite was more common in HIV-infected patients than in HIV-uninfected patients in one study.¹⁸ In a prospective cohort study conducted in South Africa from 1997 to 1999, prior to cART availability, hospitalized HIV-infected children with laboratory-confirmed influenza had more radiographic evidence of alveolar consolidation when compared with HIV-uninfected children. However, other types of bacterial complications did not vary by HIV status. Clinical outcomes including duration of hospitalization and in-hospital mortality were similar for both HIV-infected and -uninfected groups.^{18,19} The differential diagnosis for pneumonia in an HIV-infected child during the influenza season includes primary influenza pneumonia or influenza complicated by secondary bacterial pneumonia with *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Haemophilus influenzae*, the most commonly identified bacterial co-pathogens. Consideration also must be given to other potential pathogens including *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, atypical mycobacteria, endemic mycoses, and other respiratory viruses, according to the child's level of immunosuppression, potential exposures, and local epidemiology.

Diagnosis

The laboratory approach to diagnosis of influenza in HIV-infected and -uninfected children is identical. This includes rapid influenza diagnostic tests (RIDTs), immunofluorescence assays, reverse transcription-polymerase chain reaction (RT-PCR) assays, and viral culture. RT-PCR and viral culture are considered the gold standard influenza tests. Viral culture results are not immediately available and culture is not as sensitive as RT-PCR. RIDTs offer point-of-care diagnosis, but sensitivity that is substantially lower than for viral culture or RT-PCR and false-positivity—particularly when prevalence is low—limit their reliability for patient management.²⁰ Regardless of the method of laboratory diagnosis, clinical diagnosis with laboratory confirmation of influenza is important, especially in hospitalized patients and outpatients at higher risk of influenza complications.

Prevention Recommendations

Preventing Exposure

Basic personal hygiene, including hand hygiene and proper cough etiquette, are mainstays of influenza prevention. Individuals should avoid touching their eyes, nose, and mouth and avoid contact with sick individuals. Hands should be washed often with soap and water or with alcohol-based hand rub containing at least 60% alcohol, if soap and water are unavailable. Proper hand washing technique involves wetting hands with clean running water, applying soap, and rubbing and scrubbing all hand surfaces and under the fingernails for at least 20 seconds. Hands should be dried with a clean towel or air dried. When using alcohol-based hand rub, the hand rub should be applied to one hand, and the hands (including all hand surfaces and fingers) should be rubbed together until dry.

Cough etiquette directs the individual to cough or sneeze into a tissue (preferred) or, when a tissue is unavailable, into the upper sleeve or elbow rather than into the hands. A soiled tissue should be disposed of

in a waste basket. Other prevention methods include reducing crowding, maintaining a few feet of distance from others, avoiding shaking hands or hugging at gatherings, and avoiding gatherings altogether (see <http://www.cdc.gov/flu/protect/habits.htm>, <http://www.cdc.gov/handwashing>, and <http://www.cdc.gov/h1n1flu/faithbased/factsheet2.htm>).

Prolonged influenza viral shedding in a hospitalized immunocompromised patient has implications for preventing spread of influenza in the health care setting. Strategies to prevent the spread of influenza in health care facilities include use of droplet precautions by health care workers according to Healthcare Infection Control Practices Advisory Committee guidelines (see <http://www.cdc.gov/hicpac>).²¹

Preventing First Episode of Disease

Annual influenza vaccination is a cornerstone of influenza prevention, at the individual and community level.²² Past concerns about an increase in HIV viral load following influenza vaccination have not been substantiated, particularly in the presence of cART.^{11,23-27} Currently in the United States, trivalent inactivated influenza vaccine (TIV) is recommended for HIV-infected patients according to the CDC Advisory Committee on Immunization Practices (ACIP) recommendations. Multiple studies examining the immune response of HIV-infected children and adolescents on ART to TIV have shown immune responses comparable to those seen in HIV-uninfected individuals when matched for age and gender.^{26,28}

ART to maintain adequate CD4 lymphocytes is the cornerstone of adequate immune responses to vaccine.^{29,30} In a multivariate analysis of the immune response to TIV in HIV-infected children during the 1994–1995 influenza season, a higher pre-immunization CD4:CD8 ratio was associated with a greater antibody response.²⁵ Multiple studies have shown that HIV-infected individuals with depleted T lymphocytes have a suboptimal immune response to vaccines.³¹⁻³³ A randomized controlled trial of the immune response of HIV-infected children on cART to either TIV or live-attenuated influenza vaccine (LAIV) showed protective antibody titers after both vaccines (96%–98% for influenza A; 81%–88% for influenza B), with low baseline HIV viral loads correlating with improved antibody responses to both vaccines.³⁴ Although LAIV is not licensed for use in HIV-infected children, many experts would consider using it on the basis of demonstrated safety and immunogenicity in HIV-infected children on cART without CD4-defined immunosuppression.³⁵ Quadrivalent LAIV is Food and Drug Administration (FDA)-approved and is anticipated to be available in upcoming influenza seasons. ACIP recommends TIV over LAIV for HIV-infected children. Household contacts (aged 6 months and older) of HIV-infected children should receive influenza vaccine annually as a means to help protect against influenza illness.

Contraindications to use of inactivated influenza vaccine are the same for HIV-infected and HIV-uninfected individuals. A physician should be consulted before flu vaccine is administered to children who have a severe allergy to chicken eggs, have had a severe reaction to influenza vaccine in the past, are less than 6 months of age (influenza vaccine is not approved for this age group), or who have a moderate-to-severe illness with a fever (in which case the child should be vaccinated after recovery).

Antiviral chemoprophylaxis according to current CDC guidelines³⁶ is recommended for unvaccinated HIV-infected children who are close contacts of a person suspected of having or confirmed to have influenza. Selection of an antiviral drug for chemoprophylaxis should be based on current ACIP and CDC influenza antiviral recommendations and consider the antiviral susceptibility testing data for circulating influenza virus strains that can be obtained from the CDC (see <http://www.cdc.gov/flu/weekly> or <http://gis.cdc.gov/grasp/fluview/fluportaldashboard.html>). Ideally, antiviral chemoprophylaxis should be started within 48 hours of exposure to a known influenza contact. Either oseltamivir or zanamivir, part of the antiviral class of medications called neuraminidase inhibitors, are approved and recommended for chemoprophylaxis against influenza A and B viruses. Oseltamivir prophylaxis is not FDA-approved for children aged <1 year, but the American Academy of Pediatrics and CDC have issued recommendations for prophylaxis of children 3 months of age and older; zanamivir prophylaxis is not recommended for children aged <5 years (see [Table](#)). Although oseltamivir resistance has been documented previously among

circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) circulating influenza A and B viruses have been susceptible to oseltamivir.³⁶ Amantadine and rimantadine, adamantane derivatives, are approved but not currently recommended for chemoprophylaxis of influenza A viruses because of resistance of current influenza A (H3N2 and 2009 H1N1) virus strains to adamantanes.^{36,37} Amantadine (generic) and rimantadine (Flumadine®, generic) are approved to prevent only influenza A virus infection in people aged > 1 year. Because chemoprophylaxis does not totally eliminate risk of influenza illness, children who develop fever and respiratory symptoms should be evaluated by a health care provider.³⁶

Discontinuing Primary Prophylaxis

Duration of chemoprophylaxis is typically 10 days.

Treatment Recommendations

Treating Disease

Treatment of influenza in HIV-infected patients is recommended according to the ACIP and CDC guidelines. The recommended duration of treatment is 5 days, but may need to be extended in severely ill hospitalized or immunocompromised patients.³⁸ As with primary prophylaxis, selection of an antiviral drug for treatment should be based on current ACIP and CDC influenza antiviral recommendations and consider the antiviral susceptibility testing data for circulating influenza virus strains that can be obtained from the CDC (see <http://www.cdc.gov/flu/weekly> or <http://gis.cdc.gov/grasp/fluview/fluportaldashboard.html>). Currently recommended influenza antiviral medications are the neuraminidase inhibitor drugs, oseltamivir (orally administered) and zanamivir (inhaled); both are effective for treatment against influenza A and B viruses. Oseltamivir is approved for treatment of influenza in children aged ≥ 2 weeks. Although oseltamivir resistance was documented in circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) of circulating influenza A and B viruses have been susceptible to oseltamivir.³⁶ Zanamivir is approved for treatment of influenza in children aged ≥ 7 years (see [Table](#)). Alternative dosing of influenza-specific antiviral drugs and duration of therapy are under investigation. Amantadine and rimantadine, adamantane derivatives, are both effective treatments for influenza A viruses, but not influenza B viruses. Of the adamantanes, amantadine (generic) is approved to treat only influenza A viruses in people aged >1 year and rimantadine (Flumadine®; generic) is approved to treat only influenza A virus infections in people aged ≥ 13 years. However, some pediatric influenza specialists may consider rimantadine appropriate for treatment of children aged >1 year. Adamantanes are not currently recommended for treatment of influenza A because of resistance of current influenza A (H3N2 and 2009 H1N1) strains.^{36,37}

A fundamental feature of influenza in the immunocompromised host is prolonged influenza viral shedding from the respiratory tract, which may persist weeks to months in an individual with poorly controlled HIV infection.^{39,40} However, patients with well-controlled HIV on cART will have diminished influenza viral shedding, with further attenuation with antiviral treatment. During the influenza pandemic of 2009, 2009 H1N1 viral RNA was detectable by RT-PCR for a median of 4 days (range 4–5) in 5 HIV-infected, oseltamivir-treated children, compared with a median of 8 days (range 8–13) in 10 HIV-infected, oseltamivir-untreated children.¹⁵

Monitoring of Adverse Events including IRIS

Clinicians should take into account patients' age, weight, renal function, history of seizures, level of immunosuppression, presence of other medical conditions, and potential drug interactions when considering administration of influenza antiviral medications.³⁶

Zanamivir: Because of cases of respiratory deterioration manifested as decreased forced expiratory volume or bronchospasm in patients with asthma or chronic obstructive pulmonary disease, zanamivir is not recommended for treatment of patients with underlying pulmonary disease. In clinical treatment studies

involving patients with uncomplicated influenza, common adverse events were similar in those treated with inhaled zanamivir and those treated with inhaled placebo.^{36,38}

Oseltamivir: For patients with creatinine clearance 10–30 mL/min, a reduction in chemoprophylaxis dosage to 75 mg every other day and in treatment dosage to 75 mg once daily is recommended. Pharmacokinetic (PK) data are limited for dosing recommendations for patients with severe renal insufficiency on dialysis. In studies of adults and children, mild nausea and vomiting has been the most common side effect of treatment with oseltamivir;^{41,42} however, that can be somewhat alleviated if the medication is taken with food.⁴³ Despite earlier post-market reports of transient neuropsychiatric events manifested as self-injury or delirium in Japan,⁴⁴ more recently, oseltamivir has not been associated with increased risk of neuropsychiatric events.⁴⁵ The FDA recommends close monitoring for abnormal behavior in patients treated with oseltamivir.⁴³ The FDA and CDC also recommend that clinicians and pharmacists pay careful attention to the possibility of dosing errors in young children.⁴⁶

Amantadine: For patients with creatinine clearance <50 mL/min, the following dosage frequency reductions are recommended: 30 to 50 mL/min - once daily; 15 to 29 mL/min - once every 48 hours; <15 mL/min - once weekly. These patients should be observed carefully for adverse reactions that would necessitate a further decrease in dose.^{36,47} Because an increased incidence of seizures has been noted in patients with a history of seizure disorders exposed to amantadine, such patients should be observed for increased seizure activity when given the drug.^{36,48}

Rimantadine: For patients with creatinine clearance <10 mL/min, a reduction of dosage to 100 mg/day is recommended. Patients with any degree of renal insufficiency, including older individuals, should be carefully observed for adverse reactions necessitating a further decrease in dose. Also, in patients with severe hepatic dysfunction, a reduction in dosage to 100 mg/day is recommended.^{36,49} Seizure or seizure-like activity was seen in patients taking rimantadine who had a history of seizure disorders and were not taking anticonvulsants.⁵⁰

Patients aged ≤18 years with suspected influenza should not be given aspirin or aspirin-containing products such as bismuth subsalicylate (Pepto Bismol) because of the risk of Reye syndrome. In such cases, it is recommended that fever be treated with other antipyretics such as acetaminophen or non-steroidal anti-inflammatory medications.⁵¹

Drug Interactions: Clinical data are limited with respect to drug interactions between zanamivir or oseltamivir and antiretroviral drugs, and no clinical trials to date have evaluated the safety or efficacy of using combinations of different classes of influenza antiviral drugs.³⁶ However, information derived from pharmacology and PK studies of oseltamivir suggests that clinically significant drug interactions are unlikely, and zanamivir is not a substrate nor does it affect cytochrome P450 (CYP450) isoenzymes; no clinically significant drug interactions are predicted based on *in vitro* studies.

Managing Treatment Failure

Clinicians developing management plans in response to treatment failure or severe illness associated with influenza viral infections can consider changes in dosing or route of administration, increasing duration of therapy, or tailoring therapy based on viral resistance. Patients who are severely ill and hospitalized or who are immunosuppressed may require longer treatment.³⁸ In treating severely ill patients with avian influenza A (H5N1), doubling of the dose of oseltamivir (e.g., 150 mg twice daily in adults) was well tolerated in one case report⁵² and may be more effective.⁵³ For oseltamivir-resistant influenza virus infection, treatment under compassionate use and Emergency Act Authorization using nebulized⁵⁴ and intravenous (IV) zanamivir and IV peramivir have been described. Although the Emergency Act Authorization for use of these drugs through these routes of administration has expired, clinical trials of IV zanamivir, peramivir, and oseltamivir are under way through the National Institutes of Health. Clinicians interested in learning more about these trials of IV antiviral products should go to the <http://www.clinicaltrials.gov> website.

Zanamivir: IV zanamivir has occasionally been used as therapy for patients with proven resistance because of the H275Y mutation in neuraminidase. The H275Y mutation is associated with no change in susceptibility to zanamivir, but high-level oseltamivir resistance and intermediate-level resistance to peramivir, an investigational neuraminidase inhibitor.⁵⁵ IV zanamivir was previously used to treat cases of oseltamivir-resistant 2009 H1N1 infection, although it is not approved for this use. In one case report, an 18-month-old child with relapsed hematologic malignancy was admitted for a stem cell transplant and was started on oseltamivir early in the hospital course after developing cough and fever and being diagnosed with influenza A virus infection. After the child was diagnosed with 2009 H1N1 virus and experienced clinical deterioration, IV zanamivir was administered on a compassionate use basis (GlaxoSmithKline), 320 mg (20 mg/kg per dose) every 12 hours. Sequence analysis of the neuraminidase gene from virus detected in endotracheal aspirates demonstrated absence of H275Y mutation on day 2, but presence of the mutation beginning on day 13. Although this patient died on hospital day 57, administration of IV zanamivir was associated with a logarithmic drop in 2009 H1N1 viral RNA levels.⁵⁶ In another case report, a 10-year-old girl with acute lymphoblastic leukemia and PCR-documented 2009 pandemic influenza A (H1N1) infection failed oseltamivir therapy and had progressive respiratory clinical deterioration leading to intubation. The H275Y neuraminidase mutation was detected and the patient was changed to IV zanamivir for 15 days (600 mg every 12 hours) under an emergency investigational new drug application. Treatment with IV zanamivir was associated with a substantial decrease in influenza A viral loads to undetectable levels by PCR testing and the patient was weaned off the ventilator approximately 3 weeks after zanamivir initiation. The patient tolerated zanamivir well with no adverse effects.⁵⁷

Peramivir: Both adults and children with severe, progressively worsening 2009 H1N1 influenza viral pneumonia and respiratory failure experienced recovery associated with administration of IV peramivir, an investigational neuraminidase inhibitor, despite most having received oseltamivir therapy. Administration of the drug was made possible through the Emergency Investigational New Drug (eIND) regulations. From April through October 2009, in 20 adults and 11 children aged <18 years who received oseltamivir for a median of 10 days (range 1–14 days), the 14-, 28-, and 56-day survival rates were 76.7%, 66.7%, and 59.0%, respectively. The adult dosage was 600 mg IV once daily with adjustments for renal impairment, and the pediatric dose ranged from 6 mg/kg to 12 mg/kg, not to exceed 600 mg IV per day. Seventeen of 31 patients continued oseltamivir administration after initiating peramivir. Survival was associated with earlier administration of peramivir, on hospital days 2 to 8, compared with hospital days 10 to 16 in those who died. Delay in administration of the drug was mainly secondary to a delay in requesting the drug after hospitalization. The investigational drug was generally well tolerated with no reports of associated serious adverse events. Peramivir has been approved in Japan and South Korea and is undergoing U.S. Phase III trials in hospitalized patients with influenza.⁵⁸ It is important to reiterate that for patients with the H275Y mutation, peramivir is not recommended because of associated intermediate-level resistance.

Preventing Recurrence

See sections [Preventing Exposure](#) and [Preventing First Episode of Disease](#).

Discontinuing Secondary Prophylaxis

Not applicable.

References

1. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. *Lancet Infect Dis*. Apr 2007;7(4):257-265. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17376383>.
2. Cox NJ, Subbarao K. Influenza. *Lancet*. Oct 9 1999;354(9186):1277-1282. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10520648>.
3. Hall CB, Douglas RG, Jr. Nosocomial influenza infection as a cause of intercurrent fevers in infants. *Pediatrics*. May 1975;55(5):673-677. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1168894>.

4. Giannella M, Alonso M, Garcia de Viedma D, et al. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. *Clin Microbiol Infect*. Aug 2011;17(8):1160-1165. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20946412>.
5. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis*. Aug 15 2009;200(4):492-500. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19591575>.
6. Klimov AI, Rocha E, Hayden FG, Shult PA, Roumillat LF, Cox NJ. Prolonged shedding of amantadine-resistant influenzae A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. *J Infect Dis*. Nov 1995;172(5):1352-1355. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7594676>.
7. Frank AL, Taber LH, Wells CR, Wells JM, Glezen WP, Paredes A. Patterns of shedding of myxoviruses and paramyxoviruses in children. *J Infect Dis*. Nov 1981;144(5):433-441. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6273473>.
8. Bridges CB, Fry A, et al. Influenza. In: D.L. H, ed. *Control of Communicable Diseases Manual*. 19th edition. Washington, DC 2008:315-331.
9. Youzbashi E, Marschall M, Chaloupka I, Meier-Ewert H. [Distribution of influenza C virus infection in dogs and pigs in Bavaria]. *Tierärztliche Praxis*. Aug 1996;24(4):337-342. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9012016>.
10. Matsuzaki Y, Sugawara K, Mizuta K, et al. Antigenic and genetic characterization of influenza C viruses which caused two outbreaks in Yamagata City, Japan, in 1996 and 1998. *J Clin Microbiol*. Feb 2002;40(2):422-429. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11825952>.
11. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. Aug 6 2010;59(RR-8):1-62. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20689501>.
12. Dolin R. Editorial commentary: Perspectives on the role of immunization against influenza in HIV-infected patients. *Clin Infect Dis*. Jan 1 2011;52(1):147-149. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21148533>.
13. Neuzil KM, Coffey CS, Mitchel EF, Jr., Griffin MR. Cardiopulmonary hospitalizations during influenza season in adults and adolescents with advanced HIV infection. *J Acquir Immune Defic Syndr*. Nov 1 2003;34(3):304-307. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14600576>.
14. Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. *Arch Intern Med*. Feb 12 2001;161(3):441-446. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11176770>.
15. Feiterna-Sperling C, Edelmann A, Nickel R, et al. Pandemic influenza A (H1N1) outbreak among 15 school-aged HIV-1-infected children. *Clin Infect Dis*. Dec 1 2010;51(11):e90-94. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21039216>.
16. Noguera-Julian A, Provens AC, Soler-Palacin P, et al. Pandemic influenza a (2009 H1N1) in human immunodeficiency virus-infected catalan children. *Pediatr Infect Dis J*. Feb 2011;30(2):173-175. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20802374>.
17. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. *N Engl J Med*. Jul 6 2006;355(1):31-40. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16822994>.
18. Madhi SA, Ramasamy N, Bessellar TG, Saloojee H, Klugman KP. Lower respiratory tract infections associated with influenza A and B viruses in an area with a high prevalence of pediatric human immunodeficiency type 1 infection. *Pediatr Infect Dis J*. Apr 2002;21(4):291-297. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12075759>.
19. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med*. Aug 15 1992;117(4):314-324. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1637028>.
20. Centers for Disease C, Prevention. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus - United States, 2009. *MMWR Morb Mortal Wkly Rep*. Aug 7 2009;58(30):826-829. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19661856>.
21. Siegel JD, Rhinehart E, Jackson M, Chiarello L, Health Care Infection Control Practices Advisory C. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. *Am J Infect Control*. Dec 2007;35(10 Suppl 2):S65-164. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18068815>.
22. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-

- related morbidity among household contacts. *JAMA*. Oct 4 2000;284(13):1677-1682. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11015798>.
23. Sullivan PS, Hanson DL, Dworkin MS, et al. Effect of influenza vaccination on disease progression among HIV-infected persons. *AIDS*. Dec 1 2000;14(17):2781-2785. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11125897>.
 24. Zanetti AR, Amendola A, Besana S, Boschini A, Tanzi E. Safety and immunogenicity of influenza vaccination in individuals infected with HIV. *Vaccine*. Dec 20 2002;20 Suppl 5:B29-32. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12477415>.
 25. Jackson CR, Vavro CL, Valentine ME, et al. Effect of influenza immunization on immunologic and virologic characteristics of pediatric patients infected with human immunodeficiency virus. *Pediatr Infect Dis J*. Feb 1997;16(2):200-204. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9041601>.
 26. Esposito S, Tagliaferri L, Daleno C, et al. Pandemic influenza A/H1N1 vaccine administered sequentially or simultaneously with seasonal influenza vaccine to HIV-infected children and adolescents. *Vaccine*. Feb 11 2011;29(8):1677-1682. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21199699>.
 27. Keller M, Deveikis A, Cutillar-Garcia M, et al. Pneumococcal and influenza immunization and human immunodeficiency virus load in children. *Pediatr Infect Dis J*. Jul 2000;19(7):613-618. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10917218>.
 28. Levin MJ, Song LY, Fenton T, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. *Vaccine*. Aug 5 2008;26(33):4210-4217. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18597900>.
 29. Montoya CJ, Toro MF, Aguirre C, et al. Abnormal humoral immune response to influenza vaccination in pediatric type-1 human immunodeficiency virus infected patients receiving highly active antiretroviral therapy. *Mem Inst Oswaldo Cruz*. Jun 2007;102(4):501-508. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17612772>.
 30. Amendola A, Pariani E, Vigano A, et al. Influenza surveillance in a cohort of HIV-infected children and adolescents immunized against seasonal influenza. *Vaccine*. Mar 24 2010;28(15):2700-2704. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20105427>.
 31. Cagigi A, Nilsson A, Pensiero S, Chiodi F. Dysfunctional B-cell responses during HIV-1 infection: implication for influenza vaccination and highly active antiretroviral therapy. *Lancet Infect Dis*. Jul 2010;10(7):499-503. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20610332>.
 32. Chadwick EG, Chang G, Decker MD, Yogev R, Dimichele D, Edwards KM. Serologic response to standard inactivated influenza vaccine in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. Mar 1994;13(3):206-211. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8177629>.
 33. Crum-Cianflone NF, Eberly LE, Duplessis C, et al. Immunogenicity of a monovalent 2009 influenza A (H1N1) vaccine in an immunocompromised population: a prospective study comparing HIV-infected adults with HIV-uninfected adults. *Clin Infect Dis*. Jan 1 2011;52(1):138-146. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21148532>.
 34. Weinberg A, Song LY, Walker R, et al. Anti-influenza serum and mucosal antibody responses after administration of live attenuated or inactivated influenza vaccines to HIV-infected children. *J Acquir Immune Defic Syndr*. Oct 2010;55(2):189-196. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20581690>.
 35. King JC, Jr., Fast PE, Zangwill KM, et al. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. *Pediatr Infect Dis J*. Dec 2001;20(12):1124-1131. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11740317>.
 36. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza — recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. Jan 21 2011;60(1):1-24. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21248682>.
 37. Centers for Disease Control and Prevention. FluView: week ending May 20, 2010. Atlanta, GA: US Department of Health and Human Services, CDC. 2010; <http://www.cdc.gov/flu/weekly>. Accessed December 16, 2010.
 38. Glaxo Wellcome Inc. Relenza (zanamivir for inhalation) [Package insert]. 2011. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021036s027lbl.pdf.
 39. Evans KD, Kline MW. Prolonged influenza A infection responsive to rimantadine therapy in a human immunodeficiency virus-infected child. *Pediatr Infect Dis J*. Apr 1995;14(4):332-334. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7603824>.

40. King JC, Jr. Community respiratory viruses in individuals with human immunodeficiency virus infection. *Am J Med.* Mar 17 1997;102(3A):19-24; discussion 25-16. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10868138>.
41. Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet.* May 27 2000;355(9218):1845-1850. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10866439>.
42. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J.* Feb 2001;20(2):127-133. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11224828>.
43. Roche Laboratories Inc. Tamiflu (oseltamivir phosphate) capsules and oral suspension [package insert]. 2011. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021087s057lbl.pdf.
44. New concerns about oseltamivir. *Lancet.* Mar 31 2007;369(9567):1056. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17398285>.
45. Toovey S, Rayner C, Prinssen E, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug safety: an international journal of medical toxicology and drug experience.* 2008;31(12):1097-1114. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19026027>.
46. Budnitz DS, Lewis LL, Shehab N, Birnkrant D. CDC and FDA response to risk of confusion in dosing Tamiflu oral suspension. *N Engl J Med.* Nov 5 2009;361(19):1913-1914. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19797275>.
47. Soung LS, Ing TS, Daugirdas JT, et al. Amantadine hydrochloride pharmacokinetics in hemodialysis patients. *Ann Intern Med.* Jul 1980;93(1):46-49. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7396313>.
48. Atkinson WL, Arden NH, Patriarca PA, Leslie N, Lui KJ, Gohd R. Amantadine prophylaxis during an institutional outbreak of type A (H1N1) influenza. *Arch Intern Med.* Sep 1986;146(9):1751-1756. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3753115>.
49. Forest Pharmaceuticals. Flumadine syrup (rimantadine hydrochloride syrup) [Package insert]. 2006. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019649s010,019650s007lbl.pdf.
50. Soo W. Adverse effects of rimantadine: summary from clinical trials. *J Respir Dis.* 1980;10(Suppl):S26-31.
51. Food and Drug Administration. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children. 2010; <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm>. Accessed July 10, 2012.
52. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clinical pharmacokinetics.* Dec 1999;37(6):471-484. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10628898>.
53. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza AV, Abdel-Ghaffar AN, Chotpitayasunondh T, et al. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med.* Jan 17 2008;358(3):261-273. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18199865>.
54. Da Dalt L, Calistri A, Chillemi C, et al. Oseltamivir-resistant pandemic (H1N1) 2009 treated with nebulized zanamivir. *Emerg Infect Dis.* Nov 2010;16(11):1813-1815. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21029559>.
55. Baz M, Abed Y, Boivin G. Characterization of drug-resistant recombinant influenza A/H1N1 viruses selected in vitro with peramivir and zanamivir. *Antiviral Res.* May 2007;74(2):159-162. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17137644>.
56. Dulek DE, Williams JV, Creech CB, et al. Use of intravenous zanamivir after development of oseltamivir resistance in a critically ill immunosuppressed child infected with 2009 pandemic influenza A (H1N1) virus. *Clin Infect Dis.* Jun 1 2010;50(11):1493-1496. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20415572>.
57. Gaur AH, Bagga B, Barman S, et al. Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. *N Engl J Med.* Jan 7 2010;362(1):88-89. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20032317>.
58. Hernandez JE, Adiga R, Armstrong R, et al. Clinical experience in adults and children treated with intravenous peramivir for 2009 influenza A (H1N1) under an Emergency IND program in the United States. *Clin Infect Dis.* Mar 15 2011;52(6):695-706. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21367722>.

Dosing Recommendations for Chemoprophylaxis and Treatment of Influenza (page 1 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	<u>Influenza vaccine</u>	None	Note: See Figures 1 and 2 for detailed vaccines recommendations.
Primary Chemoprophylaxis Influenza A and B	<p><u>Oseltamivir for 10 days</u>^a</p> <ul style="list-style-type: none"> • Aged <3 months; not recommended^b • Aged 3 months to <1 year; 3 mg/kg body weight/dose once daily^b • Aged ≥1 to 12 years; weight-band dosing^b <ul style="list-style-type: none"> • ≤15 kg: 30 mg once-daily • >15 kg to 23 kg: 45 mg once daily • >23 kg to 40 kg: 60 mg once daily • >40 kg: 75 mg once daily • Aged ≥13 years; 75 mg once daily <p><u>Zanamivir (aged ≥5 yr) for 10 days:</u></p> <ul style="list-style-type: none"> • 10 mg (2 inhalations) once daily^c 	None	<p>Primary chemoprophylaxis is indicated for unvaccinated HIV-infected children with moderate-to-severe immunosuppression (as assessed by immunologic and/or clinical diagnostic categories) who are household contacts or close contacts of individuals with confirmed or suspected influenza. Chemoprophylaxis of vaccinated HIV-infected children with severe immunosuppression also may be indicated based on health-care provider assessment of the exposure situation. Post-exposure antiviral chemoprophylaxis should be initiated as soon as possible after exposure.</p> <p>^a Oseltamivir chemoprophylaxis duration: Recommended duration is 10 days when administered after a household exposure and 7 days after the most recent known exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the most recent known case was identified (see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm).</p> <p>^b Oseltamivir is approved by the FDA for treatment of influenza in children aged ≥2 weeks. It is not approved for prophylaxis in children aged <1 year. However, the CDC recommends that health-care providers who treat children ages ≥3 months to <1 year administer a chemoprophylaxis dose of 3 mg/kg body weight/dose once daily. Chemoprophylaxis for infants aged <3 months is not recommended unless the exposure situation is judged to be critical.</p> <p>Premature infants: Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery <38 weeks). See J Infect Dis 202 [4]:563-566, 2010 for dosing recommendations in premature infants.</p> <p>Renal insufficiency: A reduction in dose of oseltamivir is recommended for patients with creatinine clearance <30 mL/min.</p> <p>^c Zanamivir: Zanamivir is not recommended for chemoprophylaxis in children aged <5 years old.</p>

Dosing Recommendations for Chemoprophylaxis and Treatment of Influenza (page 2 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
Primary Chemoprophylaxis Influenza A (ONLY) <i>Oseltamivir-resistant, adamantane-sensitive strains</i> Based on CDC influenza surveillance; http://www.cdc.gov/flu/weekly/fluactivitysurv.htm	<u>Amantadine or rimantadine for 10 days^d:</u> <ul style="list-style-type: none"> Aged 1–9 years; 2.5 mg/kg body weight/dose twice daily (maximum dose of 150 mg/day) Aged ≥10 years <ul style="list-style-type: none"> <40 kg; 2.5 mg/kg body weight/dose twice daily ≥40 kg; 100 mg per dose twice daily (maximum dose of 200 mg/day) 		<p>^d Adamantanes: Because of resistance in currently circulating influenza A virus strains, amantadine and rimantadine are not currently recommended for chemoprophylaxis or treatment (adamantanes are not active against influenza B virus). However, potential exists for emergence of oseltamivir-resistant, adamantane-sensitive circulating influenza A strains. Therefore, verification of antiviral sensitivity of circulating influenza A strains should be done using the CDC influenza surveillance website: http://www.cdc.gov/flu/weekly/fluactivitysurv.htm</p> <p>If administered based on CDC antiviral sensitivity surveillance data, both amantadine and rimantadine are recommended for chemoprophylaxis of influenza A in children aged ≥1 yr. For <u>treatment</u>, rimantadine is only approved for use in adolescents aged ≥13 years. Rimantadine is preferred over amantadine because of less frequent adverse events. Some pediatric influenza specialists may consider it appropriate for treatment of children aged >1 year.</p> <p>Renal insufficiency: A reduction in dose of amantadine is recommended for patients with creatinine clearance <30 mL/min.</p>
Secondary Chemoprophylaxis	N/A	N/A	No role for secondary chemoprophylaxis
Treatment Influenza A and B	<u>Oseltamivir for 5 days^e:</u> <ul style="list-style-type: none"> Aged <3 months; 3 mg/kg/dose twice daily Aged 3 months to <1 year; 3 mg/kg/dose twice daily Aged ≥1 to 12 years; weight-band dosing <ul style="list-style-type: none"> ≤15 kg: 30 mg twice-daily >15 kg to 23 kg: 45 mg twice daily >23 kg to 40 kg: 60 mg twice daily >40 kg: 75 mg twice daily Aged ≥13 years; 75 mg twice daily <u>Zanamivir (aged ≥7 years) for 5 days:</u> <ul style="list-style-type: none"> 10 mg (2 inhalations) twice daily^f 	None	<p>^e Oseltamivir is FDA-approved for treatment of influenza in children aged ≥2 weeks. The CDC recommends that clinicians who treat children ages ≥3 months to <1 year administer a dose of 3 mg/kg twice daily. A dose of 3 mg/kg/dose twice daily also is recommended for infants aged <3 months.</p> <p>Premature Infants: Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants: gestational age at delivery <38 weeks. See <i>J Infect Dis</i> 202 [4]:563-566, 2010 for dosing recommendations in premature infants.</p> <p>Oseltamivir treatment duration: Recommended duration for antiviral treatment is 5 days; longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.</p> <p>Renal insufficiency: A reduction in dose of oseltamivir is recommended for patients with creatinine clearance <30 mL/min.</p> <p>^f Zanamivir: Zanamivir is not recommended for treatment in children aged <7 years.</p>

Dosing Recommendations for Chemoprophylaxis and Treatment of Influenza (page 3 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
Treatment Influenza A (ONLY) <i>Oseltamivir-resistant, adamantane-sensitive strains</i> Based on CDC influenza surveillance; http://www.cdc.gov/flu/weekly/fluactivitysurv.htm	<u>Amantadine for 5 days^d:</u> <ul style="list-style-type: none"> • Aged 1–9 years; 2.5 mg/kg body weight/dose twice daily (maximum dose of 150 mg/day) • Aged ≥10 years <ul style="list-style-type: none"> • <40 kg: 2.5 mg/kg body weight/dose twice daily • ≥40 kg: 100 mg per dose twice daily (maximum dose, 200 mg/day) <u>Rimantadine for 5 days^d:</u> <ul style="list-style-type: none"> • Aged ≥13 years; 100 mg per dose twice daily (maximum dose of 200 mg/day) 		Please see comment ^d , above, about adamantane use and resistance.

Key to Acronyms: CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration